

## REMARKS

The claims are 11 to 19.

The above amendment is responsive to points set forth in the Official Action.

In this regard, new claims 11 to 19 replace previous claims 1 to 9, respectively.

The above amendment is responsive to points set forth in the Official Action.

In the new claims, the spacing problem set forth in Official Action paragraphs 1 to 3 is not present.

With regard to Official Action paragraph 4, it is now clarified that the cyanide group is being added, as evident to one of ordinary skill in the art and from the literature cited on page 2, lines 32 to 33 of the present specification.

With regard to Official Action paragraph 5, a time of "five minutes to 20 hours" is now recited to clarify what is intended. Support is evident from page 4, line 35 of the present specification.

With regard to Official Action paragraph 6, the term "readily" has been deleted from previous claim 9 (new claim 19).

With regard to Official Action paragraph 7, claims 1-4 are rejected under 35 USC 102(b) as being anticipated by Hashimoto et al. (US 5,580,765).

This rejection is respectfully traversed.

The rejection states that Hashimoto discloses the synthesis of optically pure mandelic acid derivatives via the enzyme catalyzed addition of hydrogen cyanide followed by acidic hydrolysis and recrystallization from benzene and the use of other aromatic substrates.

This statement is not correct.

Hashimoto discloses the synthesis of optically pure mandelic acid derivates from a racemic hydroxynitrile, which is transformed into the corresponding optically active hydroxycarboxylic acid by reacting with a microorganism belonging to the genus Gordona. No enzyme catalyzed addition of hydrogen cyanide is disclosed or suggested. Also if the starting material is a mixture of an aldehyde corresponding to the nitrile and prussic acid, first the racemic nitrile is produced.

(See column 4, lines 19-21: the reaction system should be maintained nearly neutral or basic in order to racemize the hydroxynitrile)

The microorganism used for the reaction with racemic hydroxynitrile is responsible for the asymmetrical hydrolysis of the nitrile group of the racemic hydroxynitrile. (See column 2, lines 12-14: which comprises reacting a microorganism capable of asymmetrically hydrolyzing a nitrile group of a racemic hydroxynitrile; see column 2, lines 44-47).

This asymmetric hydrolysis is not an acidic hydrolysis, since this reaction takes place in nearly neutral or basic conditions.

To isolate the optically active hydroxycarboxylic acid first the microorganism is removed and then the reaction mixture is extracted. As can be seen from Example 1, the supernatant is first adjusted to pH 12, then extracted twice and in a second extraction step the aqueous layer is adjusted to pH 1.2 and extracted twice again. This is the only step performed in an acidic medium, but this is not an acidic hydrolysis.

After this extraction step, Hashimoto discloses the possibility of repeated recrystallization from benzene etc. in column 4, lines 49-50, but according to the Examples no recrystallization is performed.

Contrary to Hashimoto, according to the present invention, first optically active nitriles are produced by enzyme catalyzed addition of hydrogen cyanide to an aldehyde, then the optically active nitrile is hydrolyzed under acidic conditions to the corresponding hydroxycarboxylic acid, which is recrystallized once in an aromatic hydrocarbon, optionally in the presence of a cosolvent.

Therefore two different processes are described or disclosed.

According to Hashimoto, a racemic nitrile is transformed to the corresponding optically active hydroxycarboxylic acid by reacting with a microorganism belonging to the genus Gordona. This transformation yields D-mandelic acid and some derivatives with an optical purity of up to 100%. Therefore this kind of reaction type does not need any work up to improve the optical purity and the chemical purity. While Hashimoto discloses that it would be possible to perform repeated recrystallization, he does not disclose any example with a recrystallization step. Therefore, no one skilled in the art could conclude from Hashimoto that recrystallization would

have the effect of improving the optical purity as well as the chemical purity of the desired optically active hydroxycarboxylic acids.

On the contrary, optically active hydroxycarboxylic acids obtained after the enzyme catalyzed addition of hydrogen cyanide to obtain optically active nitriles, which are then hydrolyzed under acidic conditions as per the present invention, show an optical purity of about 89-92%ee (see page 5, line 32 to page 6, line 1 of the present specification), due to the fact that the enzyme catalyzed addition of hydrogen cyanide yields optically active nitriles with an optical purity of about 89-92%ee and since during the hydrolysis step no racemization takes place, as explained on page 5, line 30 - page 6, line 1. Therefore, a special work up was necessary to improve the optical purity as well as the chemical purity.

For the above discussed reasons, the process according to present claims 11-14 is not anticipated by or rendered obvious from Hashimoto, since the present invention and Hashimoto describe different processes to get optically active hydroxycarboxylic acids and since there is absolutely no suggestion in the Hashimoto reference that a single recrystallization step as disclosed by the present specification, could improve the optical purity as well as the chemical purity.

With regard to Official Action paragraph 8, the rejection of claim 10 is moot in view of the cancellation thereof.

Claims 1-10 are rejected under 35 USC 103(a) as being unpatentable over Hashimoto et al. (US 5,580,765) and further in view of Yu et al. (US 4,105,783).

This rejection is respectfully traversed.

Again the rejection states that Hashimoto teaches the synthesis of optically pure mandelic acid derivatives via the enzyme catalyzed addition of hydrogen cyanide followed by acidic hydrolysis and their purification by recrystallization from benzene and the use of other aromatic substrates.

This statement is not correct, as discussed above.

Further, the rejection states that according to Hashimoto the supernatant may be extracted with an organic solvent in an acidic condition, followed by repeated recrystallization from benzene etc. and that Hashimoto is silent with respect to the temperature of the nitrile hydrolysis reaction.

As has been discussed above, the hydrolysis according to Hashimoto is not an acidic one as disclosed by the present specification.

Hashimoto teaches an asymmetric hydrolysis by reacting a racemic nitrile with a microorganism in a neutral to basic aqueous medium and no acidic hydrolysis. Therefore, these two hydrolysis steps cannot be compared and are not suggestive of each other.

The extraction step according to Hashimoto is performed after the asymmetrical hydrolysis. The extraction step is therefore not a hydrolysis step. Further as can be seen from Example 1, the extraction is first performed at pH 12 and in the second step under acidic conditions.

Further the rejection states that Hashimoto teaches hydrolysis of the nitrile in an organic solvent and that it would be obvious for one skilled in the art to realize that the recrystallization could be carried out in the hydrolysis medium.

Since Hashimoto does not teach hydrolysis of the nitrile in an organic solvent, but rather in a neutral to basic aqueous medium (see claim 1, column 2, lines 24-25,) it could not have been obvious to an art skilled person that recrystallization could be carried out directly after, in a hydrolysis medium as disclosed by the present application.

According to Hashimoto, the only step which is performed in an organic solvent is the 2-step extraction, which is performed after the asymmetric hydrolysis.

According to the present invention, no extraction step is necessary, if the recrystallization is coupled to the hydrolysis step.

The rejection also states that according to Hashimoto it was obvious to choose aromatic hydrocarbons, optionally with a cosolvent for the recrystallization step. Since Hashimoto only mentions that the desired product could be recrystallized, but does not show any effect that such a recrystallization could have, it would not have been obvious to an art skilled person that the

choice of aromatic hydrocarbons, optionally with a cosolvent, would improve the optical purity as well as the chemical purity, as discussed above.

Summing up, the process according to the present invention is not obvious in view of Hashimoto, since Hashimoto discloses a different process and since there is absolutely no suggestion in Hashimoto that the optical and chemical purity of hydroxycarboxylic acids, obtained by acidic hydrolysis of optically active nitriles, which are produced by enzyme catalyzed addition of hydrogen cyanide to an aldehyde, could be improved by a single recrystallization step using aromatic hydrocarbons, optionally with a cosolvent.


For the foregoing reasons, it is apparent that the rejections on prior art are untenable and should be withdrawn.

No further issues remaining, allowance of this application is respectfully requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact undersigned at the telephone number below.

Respectfully submitted,

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